11:30 a.m.

858-5 **Effect of Gender on the Outcome of Patients With Severe Heart Failure Treated With Carvedilol: Results of the COPERNICUS Study**

Michal P. Tendera, Andrew J. Coats, Michael B. Fowler, Hugo A. Katus, Paul Mohacsi, Jean L. Rouleau, Henry Krum, Ildiko Amann-Zalan, Neil H. Shusterman, Ellen B. Roecker, Milton Packer, for the COPERNICUS Study, *Silesian School of Medicine, Katowice, Poland.*

Background: The results of the MERIT-HF trial suggested that women with heart failure (HF) respond less favorably to β-blockade than men. To further explore this observation, we evaluated the effect of gender on the response to carvedilol (CRV) in the COPERNICUS trial.
Methods: 2289 patients (1824 men, 465 women) with symptoms of CHF at rest or on minimal exertion and ejection fraction <25% were randomly assigned to placebo (PBO) or CRV for up to 29 months. Women were older than men (66 vs 63 yrs; P<0.001) and were more likely to have non-ischemic HF (42% vs 30%; P<0.001) but were similar in other baseline characteristics.
Results: Shown below are Cox model (CRV:PBO) hazard ratios, 95% CI and interaction P values:

	Men	Women	Interaction P value
All-cause mortality	0.65 (0.51-0.83)	0.65 (0.39-1.11)	0.98
Death or any hospitalization	0.79 (0.68-0.91)	0.67 (0.51-0.89)	0.98
Death or cardiovascular hospitalization	0.76 (0.65-0.90)	0.60 (0.43-0.84)	0.21
Death or HF hospitalization	0.73 (0.61-0.87)	0.57 (0.40-0.81)	0.20

Gender did not influence the frequency of adverse effects attributable to CRV (e.g., bradycardia). However, when compared with PBO, men treated with CRV were 11% less likely and women treated with CRV were 27% less likely to experience a serious adverse event (interaction P = 0.10). The risk of permanent withdrawal was lower with CRV than with PBO in both sexes (relative risk in women = 0.56 [95% CI, 0.33-0.96]; relative risk in men = 0.82 [95% CI, 0.65-1.05], interaction P=0.21).
Conclusion: In COPERNICUS women with severe HF experienced similar clinical benefits and tolerated treatment with CRV as well as men.

11:45 a.m.

858-6 **Advanced Heart Failure Patients Unable to Reach ACE Inhibitor Targets: A High Risk Population Identified During Hospitalization**

Monica R. Shah, Vic Hasselblad, Lynne W. Stevenson, Wendy A. Gattis, Mihai Gheorghiade, Robert M. Califf, Christopher M. O'Connor, *Duke Clinical Research Institute, Durham, North Carolina, Brigham and Women's Hospital, Boston, Massachusetts.*

Background-ACE inhibitors (ACEI) are generally prescribed to patients with advanced heart failure (HF) in doses lower than shown effective in clinical trials. We sought to define the advanced HF population in which ACEI could not be titrated to target doses. **Methods**-The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Chronic Congestive Heart Failure (OPTIME-CHF) enrolled 949 patients with NYHA class III-IV HF. Achieving target doses of ACEI was a predefined endpoint of the trial. **Results**-Patients unable to reach >50% ACEI target doses were older, had lower systolic blood pressure (BP), and higher creatinine. Clinical features of the patients are shown (Table). Advanced HF patients discharged on <50% ACEI had a significantly higher rate of death or hospitalization at 60 days than did patients taking >50% ACEI target doses, even after adjustment for age, NYHA class, ejection fraction (EF), creatinine, and systolic BP (odds ratio, 1.48; 95% CI, 1.04-2.10; p=0.03). **Conclusions**-Even after adjusting for clinical factors that contribute both to low ACEI dosing and higher mortality, patients on <50% ACEI target doses had worse outcomes. This suggests an inability to tolerate >50% ACEI target doses defines a large subgroup of advanced HF patients with worse prognosis that may require new treatment strategies.

Clinical Features of Patients on Low vs High Dose ACEI

Clinical Feature (median, interquartile range)	<50% ACEI Target Dose (n=305)	>50% ACEI Target Dose (n=422)	p value
Age, y	71 (60, 78)	61 (51, 73)	0.0001
SBP, mmHg	114 (102, 131)	123 (110, 136)	0.0001
Creatinine, mg/dL	1.4 (1.1, 1.7)	1.3 (1, 1.6)	0.007
Death or hosp, %	39.3%	28.1%	0.002

POSTER SESSION

1181 Genes and Heart Failure Hypertrophy

Tuesday, March 19, 2002, Noon-2:00 p.m.
Georgia World Congress Center, Hall G
Presentation Hour: Noon-1:00 p.m.

1181-141 **NOS3 Deficiency Is Associated With a Shift Toward Pro-Oxidant Gene Expression in Murine Myocardium**

Thomas P. Cappola, Brian Rah, Sarfraz A. Durrani, Amy Cernetich, Dan E. Berkowitz, Eric Hoffman, Joshua M. Hare, NHLBI Program in Genomic Applications--Hopgene, *Johns Hopkins University, Baltimore, Maryland, Center for Genetic Medicine, Children's National Medical Center, Washington, Dist. of Columbia.*

Background: Inhibition or transgenic deletion of NOS3 has adverse effects on contractile function in vitro, and leads to hypertension and left ventricular hypertrophy in vivo. A large body of data indicates that nitric oxide (NO) exerts many of its effects by interacting with a complex network of redox signaling pathways. Using a genomic approach, we tested the hypothesis that NOS3 deficiency leads to compensatory changes in the expression of redox genes in murine myocardium.
Methods: Myocardial RNA was isolated from $NOS3^{-/-}$ mice and their appropriate C57Bl/6 controls (n=3 each, age 4.0 +/- 0.5 mos.; Trizol reagent extraction method). Within each group, samples were combined in equimolar amounts resulting in single $NOS3^{-/-}$ and control RNA pools. Duplicate in vitro transcriptions were performed on each pool to form 2 $NOS3^{-/-}$ and 2 control cRNA probes that were each hybridized with a murine Affymetrix MG74A chip containing ~6,000 genes and ~6000 ESTs. Relative expression of a predefined group of oxidases, the superoxide dismutases (SOD), catalase, and members of the glutathione pathway were compared among the $NOS3^{-/-}$ and control pools. Statistical significance was determined using a Monte-Carlo method.
Results: Of the 40 genes examined, seven were under-expressed in $NOS3^{-/-}$ myocardium, including mitochondrial and cytosolic SOD, glutathione transferase, and five nuclear-encoded subunits of cyctochrome C oxidase (complex IV). In contrast, only extracellular SOD was over-expressed.
Conclusions: These data indicate a shift in myocardial gene transcription toward a pro-oxidant state in the absence of NOS3. In addition to increasing ventricular afterload, NOS3 deficiency may promote ventricular hypertrophy by promoting oxidative stress within the myocardium.

1181-142 **Compensatory Electrical Remodeling in Hearts of Transgenic Mice That Overexpress the Ca2+ Channel Alpha 1C Subunit**

Ilona Bodi, James N. Muth, Gyula Varadi, Natasha N. Petrashevskaya, Arnold Schwartz, *University of Cincinnati, Cincinnati, Ohio.*

Background: Prolongation of the action potential duration (APD) and a reduction of the transient outward K^+ current (I_{to}) are thought to be hallmarks of hypertrophy. A model in which the α_1 subunit of the L-voltage-dependent calcium channel is over-expressed in transgenic mice offers an opportunity to study this phenomenon in detail.
Methods: We used the whole-cell patch-clamp technique, radioligand binding and retrograde perfused hearts to characterize this model at the cell and organ level.
Results: Electrophysiological analysis in ventricular myocytes isolated from transgenic (Tg) and nontransgenic (Ntg) mice at 4-month of age (mild hypertrophy) demonstrated a slight decrease in the APD at 90% repolarization (APD_{90}) and an up-regulation of the L-type Ca^{2+}-current and dihydropyridine binding. The changes were accompanied by a small increase in I_{to} density without altering the steady-state inactivation. No change was detected in the protein expression level of Kv4.3 and 4.2 up to 8-months of age. Kv1.4 was up-regulated in Tg hearts from 8-month old mice. In cardiomyocytes from 10-12 month old Tg mice (hypertrophied and failing) APD_{90} was longer compared to Ntgs; 4-aminopyridine evoked spontaneous triggered activity and hearts revealed a very low basal contractility. At -140 mV no significant change was observed between Tg and Ntg cells in the inwardly rectifying potassium current. The I_{to} up-regulation may exert a compensatory function for the high Ca^{2+} induced prolongation of APD. At 10-12 months the Tg mice showed a slight decrease (41.4%±6.9, $P<0.05$, n=3) in Kv4.2 consistent with a decrease in I_{to}.
Conclusion: This study demonstrates the complexity of ion current changes in a model of hypertrophy and failure, and the difficulty of using the APD as a hallmark of cardiac hypertrophy. The data also suggest that increased $[Ca^{2+}]_i$ may be an important factor not only in triggering disease but in electrical remodeling.

1181-143 **A Novel Efficient Percutaneous Myocardial Gene Delivery System**

Ronen Beeri, Luis J. Guerrero, Suzanne Sullivan, Gregory Supple, Robert A. Levine, Roger J. Hajjar, *Massachusetts General Hospital, Boston, Massachusetts.*

Manipulating gene expression in the failing heart has therapeutic promise, but up to now efficient and homogeneous cardiac gene delivery has required an open-chest approach. Critical conditions to maximize percutaneously delivered gene expression include prolonging the exposure to the viral vector and enhancing its myocardial uptake across the endothelial barrier. Ultrasound-induced disruption of echo contrast microbubbles enhances endothelial crossing. We planned to maximize vector delivery with bubbles by injection into the aortic root with brief balloon occlusion above the sinuses, while prolonging diastole and vasodilating with acetylcholine (ACh).
Methods: In 20 male rats an angioplasty balloon catheter was positioned just above the aortic valve via the right carotid artery. The LV was imaged in long axis view with an esophageal echo catheter (AcuNav). In 5 rats, the balloon was inflated and 1.5 μg ACh